# European Journal of Organic Chemistry

Supporting Information

Passerini and Ugi Reactions Involving Kinetically Unstable Isocyanides

Alexandre Quelhas, Houda Gazzeh, Thierry Roisnel, Yann Trolez, and Jean-Claude Guillemin\*

# Supporting Information

## TABLE OF CONTENTS

<u>1-</u>	EXPERIMENTAL PROCEDURES	2
<u>2-</u>	NMR SPECTRA	
<u>3-</u>	CRYSTALLOGRAPHIC DATA	23

#### **1- EXPERIMENTAL PROCEDURES**

#### **General Information**

All reactions were carried out under dinitrogen with magnetic stirring. All chemicals were obtained from commercial suppliers and used without further purification. Reagent grade solvents were used without purification for all extractions and workup procedures. The TLC were run on 0.25 mm silica gel plates (60-F254). Purifications with column chromatography were performed on silica gel 60 (43–60  $\mu$ m) using dichloromethane (DCM) to prepare the silica gel. Yields refer to chromatographically and spectroscopically pure compounds. NMR measurements were recorded on Bruker Avance at 23 °C, 400 MHz for proton and 100 MHz for carbon. Chemical shifts ( $\delta$ ) are reported in ppm and coupling constants (J) are reported in Hz. The following abbreviations are used to describe multiplicity; br-broad, s- singlet, d- doublet, t- triplet, q- quartet, m- multiplet. Short wave UV radiation (245 nm) and KMnO<sub>4</sub> were used to visualize components. HRMS spectra were recorded on a Maxis 4G and Q-Exactive, depending on the targeted structure.

N-Propargylformamide,<sup>[1]</sup> Vinylisocyanide **1**,<sup>[2]</sup> Propargylisocyanide **2**,<sup>[3]</sup> Allenylisocyanide **3**<sup>[4]</sup> and 4lodobenzyl azide <sup>[5]</sup> have been prepared as previously reported. The syntheses of the three isocyanides are recalled.

**Vinylisocyanide (1).** Vinylformamide (0.71 g, 10 mmol), *p*-toluenesulfonyl chloride (3.81 g, 20 mmol), duroquinone (20 mg) and trioctylamine (7.07 g, 20 mmol) were introduced into a one-necked round bottom flask equipped with a stirring bar. The flask was fitted on a vacuum line (4 mbar) equipped with two U-tubes with stopcocks. The first trap was immersed in a cold bath cooled to -90 °C. The apparatus was evacuated, and the mixture allowed to warm to 80 °C for about 1 h. The isocyanide was thus evacuated from the reaction mixture as it was formed and condensed in the trap. At the end of the reaction, the trap was allowed to warm to room temperature, and pure isocyanide **1** was condensed in the second trap immersed in a bath cooled to -90 °C (38% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.91 (ddt, 1H, *J* = 15.5, 8.5, 2.3 Hz), 5.61 (ddt, 1 H, *J* = 15.5, 3.2, 0.4 Hz), 5.37 (ddt, 1H, *J* = 8.5,

<sup>&</sup>lt;sup>[1]</sup> E. N. Gate, M. D. Threadgill, M. F. G. Stevens, D. Chubb, L. M. Vickers, S. P. Langdon, J. A. Hickman, A. Gescher, *J. Med. Chem.* **1986**, *29*, 1046–1052.

<sup>&</sup>lt;sup>[2]</sup> A. Chrostowska, A. Matrane, D. Maki, S. Khayar, H. Ushiki, A. Graciaa, L. Belachemi, J.-C. Guillemin, *ChemPhysChem* **2012**, *13*, 226–236.

<sup>&</sup>lt;sup>[3]</sup> J. W. Zwikker, R. W. Stephany, Synth. Commun. **1973**, *3*, 19-23.

<sup>&</sup>lt;sup>[4]</sup> H. Møllendal, S. Samdal, A. Matrane, J.-C. Guillemin, J. Phys. Chem. A **2011**, 115, 7978–7983.

<sup>&</sup>lt;sup>[5]</sup> M. Tanno, S. Sueyoshi, S. Kamiya, *Chem. & Pharm. Bull.* **1982**, *30*, 3125–3132.

6.2, 0.4 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.4 (t (quadr. moment), *J* = 6.3 Hz), 121.0, 119.1 (t (quadr. moment), *J* = 12.1 Hz).

**Propargylisocyanide (2)** was prepared by the same approach starting from propargylformamide but without using duroquinone and with a vacuum of 1 mbar. (50% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.23 (dt, 2H, *J* = 2.6, 2.3 Hz), 2.44 (t, 1 H, *J* = 2.6 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.8 (t (quadr. moment), *J* = 4.2 Hz), 74.0, 73.5, 31.5 (t (quadr. moment), *J* = 8.7 Hz).

Allenylisocyanide (3). In a 100 mL one-necked, round bottom flask equipped with a stirring bar were introduced propargylformamide (2.05 g, 25 mmol), *p*-toluenesulfonyl chloride (6.67 g, 35 mmol), and trioctylamine (17.7 g, 50 mmol). The flask was attached to a vacuum line equipped with three traps with stopcocks. The first and second traps each contained 2 g of KOH powder. The first trap was immersed in a liquid nitrogen bath and the apparatus was then evacuated to 1 mbar. The mixture was slowly heated to 80 °C for about 1 h. Propargylisocyanide **2** was then evacuated from the reaction mixture as it was formed, and condensed in the trap. At the end of the reaction, this first trap was isolated with stopcocks from the vacuum line and allowed to warm to room temperature for about 2 min. The mixture turned black quite rapidly. The low boiling compounds were then revaporized in vacuo and condensed in the second trap cooled at -90 °C. The stopcocks of this trap were closed, and the heterogeneous mixture was allowed to warm to room temperature and maintained at this temperature for 2 min. The mixture again turned black quite rapidly. The revaporization and condensation in the third trap cooled at -90 °C gave the expected product **3** (39% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.95 (t, 1H, *J* = 6.5 Hz), 5.45 (dt, 2H, *J* = 6.5, 1.8 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  210.7, 166.5 (t (quadr. moment), *J* = 6.3 Hz), 86.1 (t (quadr. moment), *J* = 15.3 Hz), 85.9.

Isocyanides **1-3** in pure form were stored in a cell immersed in dry ice or liquid nitrogen, and diluted under dinitrogen in a solvent cooled to -50 ° C before use in a subsequent reaction. They can only be handled by trap-to-trap manipulation.

General procedure for the preparation of  $\alpha$ -amino amides in methanol. In a three-neck round bottom flask under dinitrogen containing a solution stirred at 0 °C of amine (7.7 mmol, 1.0 equiv.), formaldehyde (37% in water, 7.7 mmol, 1.0 equiv.), acetic acid (7.7 mmol, 1.0 equiv.) in MeOH (8 mL), was added a cooled solution of isocyanide (7.7 mmol, 1 equiv.) in MeOH (12 mL). The mixture was stirred overnight at room temperature. The yellowish solution was concentrated under reduced pressure and the liquid obtained was diluted in dichloromethane (20 mL), washed with a saturated aqueous solution of NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography (SiO<sub>2</sub>, eluent: DCM/MeOH from 100 to 95:5).

*N*-(*tert*-butyl)-*N*-(2-oxo-2-(vinylamino)ethyl)acetamide (4a). Reaction with *t*-butylamine. White solid, mp: 90 °C. Yield: 1.81 g, 49%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.90 (br s, 1H), 6.94 (ddd, 1H, *J* = 15.9, 10.9, 8.7 Hz), 4.67 (dd, 1H, *J* = 15.9, 0.9 Hz), 4.49 (dd, 1H, *J* = 8.7, 0.9 Hz), 4.03 (s, 2H), 2.11 (s, 3H), 1.45 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.8, 167.6, 128.0, 96.9, 57.9, 50.0, 29.1, 25.5; HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>Na: 221.1266, found: 221.1266.

*N*-(*tert*-butyl)-*N*-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)acetamide (4b). Reaction with *t*-butylamine. Yellow solid, mp: 50 °C. Yield: 0.86 g, 50%, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.39 (d, 1H, *J* = 4.4 Hz), 4.09 (dd, 2H, *J* = 5.4, 2.5 Hz), 3.99 (s, 2H), 2.25 (t, 1H, *J* = 2.5 Hz), 2.10 (s, 3H), 1.45 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.6, 169.7, 78.9, 72.2, 58.0, 50.1, 29.3, 28.9, 25.5; HRMS (ESI) m/z [M+Na]<sup>+</sup>calcd. for  $C_{11}H_{18}N_2O_2Na: 233.1266$ , found: 233.1266.

*N*-(*tert*-butyl)-*N*-(2-oxo-2-(propa-1,2-dien-1-ylamino)ethyl)acetamide (4c). Reaction with *t*-butylamine. Orange solid, mp: 94 °C (dec). Yield: 1.43 g, 38%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.08 (br s, 1H), 6.98 (dt, 1H, *J* = 10.0, 6.4 Hz), 5.34 (d, 2H, *J* = 6.4 Hz), 4.03 (s, 2H), 2.13 (s, 3H), 1.46 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 202.1, 172.8, 167.4, 93.4, 86.7, 58.1, 50.2, 29.1, 25.6; HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd. for  $C_{11}H_{18}N_2O_2Na$ : 233.1266, found: 233.1266.

*N*-allyl-*N*-(2-oxo-2-(vinylamino)ethyl)acetamide (4d). Reaction with allylamine. Yellow solid, mp: 62 °C. Yield: 1.29 g, 31% (Cis/Trans:4/6). Cis isomer: <sup>1</sup>H NMR (400 MHz, DMSO-*d<sub>6</sub>*) δ 10.06 (br d, 1H, *J* = 10.2 Hz), 6.85–6.72 (m, 1H), 5.68 (ddt, 1H, *J* = 17.2, 10.2, 5.8 Hz), 5.18–5.08 (m, 2H), 4.67 (d, 1H, *J* = 16.0 Hz), 4.35 (d, 1H, *J* = 8.8 Hz), 3.98 (s, 2H), 3.86 (dt, 2H, *J* = 5.8, 1.5 Hz), 1.94 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d<sub>6</sub>*) δ 170.4, 166.5, 133.7, 128,9, 116.9, 95.6, 50.0, 48.2, 21.3. Trans isomer: <sup>1</sup>H NMR (400 MHz, DMSO-*d<sub>6</sub>*) δ 9.86 (br d, 1H, *J* = 10.1 Hz), 6.85–6.72 (m, 1H), 5.86 (ddt, 1H, *J* = 17.1, 10.5, 5.3 Hz), 5.18–5.08 (m, 2H), 4.65 (d, 1H, *J* = 15.9 Hz), 4.31 (d, 1H, *J* = 8.9 Hz), 3.97 (dt, 2H, *J* = 5.3, 1.6 Hz), 3.88 (s, 2H), 2.01 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d<sub>6</sub>*) δ 170.4, 166.6, 133.9, 129.1, 116.3, 94.9, 51.9, 48.2, 20.9. HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Na: 205.0948, found: 205.0947.

*N*-allyl-*N*-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)acetamide (4e). Reaction with allylamine. Orange solid, mp: 54 °C. Yield: 1.37 g, 39%, (Cis/Trans:4/6). Cis isomer: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.51 (t, 1H, *J* = 5.6 Hz), 5.70–5.61 (m, 1H), 5.17–5.06 (m, 2H), 3.88 (s, 2H), 3.86 (dd, 2H, *J* = 5.4, 2.5 Hz), 3.84–3.82 (m, 2H), 3.04 (t, 1H, *J* = 2.5 Hz), 1.93 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 171.3, 168.7, 133.6, 117.5, 81.1, 73.4, 50.5, 48.8, 28.5, 21.6. Trans isomer <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.32 (t, 1H, *J* = 5.6 Hz), 5.87–

5.78 (m, 1H), 5.17–5.06 (m, 2H), 3.90 (dt, 2H, J = 5.2, 1.5 Hz), 3.83 (dd, 2H, J = 5.6, 2.4 Hz), 3.81 (s, 2H), 3.01 (t, 1H, J = 2.4 Hz), 2.00 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ )  $\delta$  171.4, 168.8, 133.8, 116.9, 81.4, 73.2, 52.1, 48.4, 28.3, 21.3. HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Na: 217.0948, found: 217.0948.

General procedure for the preparation of  $\alpha$ -acyloxy amides (5a-5c). To a 0 °C cooled solution of formaldehyde (37% in water, 21.6 mmol, 1.0 equiv.) in dichloromethane (2 mL), was added under dinitrogen a cooled solution of isocyanide (5.4 mmol) in dichloromethane (4 mL). After 3 minutes under stirring at 0 °C, acetic acid (5.4 mmol, 1 equiv.) was added to the mixture and the resulting solution was allowed to reach room temperature. The reaction was stirred at room temperature overnight. The biphasic mixture was concentrated in vacuo and the liquid obtained was diluted with dichloromethane and few drops of brine. The aqueous phase was collected and washed with dichloromethane. The organic phases were gathered, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting liquid was purified by column chromatography (SiO<sub>2</sub>, eluent: DCM/MeOH from 100 to 95:5) and concentrated under reduced pressure.

**2-Oxo-2-(vinylamino)ethyl acetate (5a).** Colorless liquid. Yield: 0.52 g, 45%. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.77 (br s, 1H), 6.95 (ddd, 1H, *J* = 15.9, 10.8, 8.8 Hz), 4.76 (dd, 1H, *J* = 15.9, 0.8 Hz), 4.55 (s, 2H), 4.51 (br d, 1H, *J* = 8.8 Hz), 2.16 (s, 3H). <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  169.9, 165.1, 128.1, 97.2, 63.2, 21.0; HRMS (ESI) m/z [M+H]<sup>+</sup> calcd. for C<sub>6</sub>H<sub>9</sub>NO<sub>3</sub>Na: 166.0475, found: 166.0476.

**2-Oxo-2-(prop-2-yn-1-ylamino)ethyl acetate (5b).** White solid, mp: 51 °C. Yield: 0.66 g, 41%. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 6.40 (br s, 1H), 4.53 (s, 2H), 4.08 (dd, 2H, *J* = 5.6, 2.6 Hz), 2.30 (t, 1H, *J* = 2.6 Hz), 2.15 (s, 3H). <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 169.9, 167.2, 79.8, 71.8, 63.4, 29.1, 21.1; HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd. for C<sub>7</sub>H<sub>9</sub>NO<sub>3</sub>Na: 178.0475, found: 178.0478.

**2-Oxo-2-(propa-1,2-dien-1-ylamino)ethyl acetate (5c).** Viscous oil. Yield: 0.52 g, 62%. <sup>1</sup>H NMR (400 MHz, acetone-*d6*)  $\delta$  8.65 (br s, 1H), 6.94 (dt, 1H, *J* = 9.5, 6.6 Hz), 5.26 (d, 2H, *J* = 6.6 Hz), 4.58 (s, 2H), 2.07 (s, 3H). <sup>13</sup>C NMR (100 MHz, acetone-*d6*)  $\delta$  203.4, 170.4, 165.6, 93.6, 85.5, 63.1, 20.5; HRMS (ESI) m/z [M+H]<sup>+</sup> calcd. for C<sub>7</sub>H<sub>10</sub>NO<sub>3</sub>: 156.0655, found: 156.0655.

*N*-(*tert*-butyl)-*N*-(2-oxo-2-((1-(phenylthio)ethyl)amino)ethyl)acetamide (6a) (Method A). To a solution of *N*-(*tert*-butyl)-*N*-(2-oxo-2-(vinylamino)ethyl)acetamide 4a (200 mg, 1.01 mmol, 1.0 equiv.) in dioxane (1.5 mL) was added at room temperature thiophenol (121 mg, 1.09 mmol, 1.1 equiv.) and 2 drops of piperidine. The mixture was stirred at reflux under dinitrogen and monitored by TLC (DCM/MeOH (95:5)). After 5 hours at reflux, the mixture was cooled at room temperature and diluted with  $Et_2O$  (3.0 mL) and a 5% aqueous solution of NaHCO<sub>3</sub> (3.5 mL). The organic phase was collected and washed with

a 5% aqueous solution of NaHCO<sub>3</sub> (2 mL), H<sub>2</sub>O (2 mL), dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. Purification by column chromatography (SiO<sub>2</sub>, eluent: DCM/MeOH from 100 to 95:5) gave compound **6a** as a white solid, mp: 110 °C. (88 mg, 28% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.42–7.39 (m, 2H), 7.31–7.24 (m, 3H), 6.22 (br d, 1H, *J* = 9.4 Hz), 5.68 (dq, 1H, *J* = 9.4, 6.7 Hz), 3.95–3.70 (m, 2H), 1.85 (s, 3H), 1.53 (d, 3H, *J* = 6.7 Hz), 1.30 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.4, 168.8, 132.6, 132.0, 129.3, 127.9, 57.9, 52.0, 50.1, 28.8, 25.1, 22.1; HRMS (ESI) calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>NaS [M+Na]<sup>+</sup>: 331.1451, found: 331.1454.

*N*-(*tert*-butyl)-*N*-(2-oxo-2-((2-(phenylthio)ethyl)amino)ethyl)acetamide (6b) (Method B). To a solution of *N*-(*tert*-butyl)-*N*-(2-oxo-2-(vinylamino)ethyl)acetamide **4a** (200 mg, 1.01 mmol, 1.0 equiv.) in dioxane (1.5 mL) was added under dinitrogen, thiophenol (121 mg, 1.09 mmol, 1.1 equiv.). The mixture was stirred at reflux and monitored by TLC (DCM/MeOH (95:5)). After 23 hours at reflux, the starting acetamide was not fully-consumed. The mixture was cooled at room temperature and diluted with Et<sub>2</sub>O (10 mL) and H<sub>2</sub>O (7 mL). The aqueous phase was collected and washed with Et<sub>2</sub>O (7 mL). The organic layers were gathered, washed with brine (5 mL) dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The product was purified by column chromatography (SiO<sub>2</sub>, eluent: DCM/MeOH from 100 to 98:2) to give a mixture of 92% of *N*-(*tert*-butyl)-*N*-(2-oxo-2-((2-(phenylthio)ethyl)amino)ethyl)acetamide **6a**. Yellow solid, mp: 84 °C. Yield: 241 mg, 71%. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.39–7.20 (m, 5H), 6.43 (br s, 1H), 3.91 (s, 2H), 3.48 (dt, 2H, *J* = 6.4, 6.2 Hz), 3.09 (t, 2H, *J* = 6.4 Hz), 2.03 (s, 3H), 1.43 (s, 9H). <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  172.7, 170.3, 135.4, 130.3, 129.7, 127.1, 58.1, 50.6, 38.6, 34.1, 29.0, 25.6; HRMS (ESI) calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>NaS [M+Na]<sup>\*</sup>: 331.1451, found: 331.1454.

*N*-(*tert*-butyl)-*N*-(2-((2-(hexylthio)ethyl)amino)-2-oxoethyl)acetamide (6c) (Method B). To a solution of *N*-(*tert*-butyl)-*N*-(2-oxo-2-(vinylamino)ethyl)acetamide **4a** (200 mg, 1.01 mmol, 1.0 equiv.) in dioxane (1.5 mL) was added at room temperature 1-hexanethiol (128 mg, 1.09 mmol, 1.1 equiv.) and 2 drops of piperidine. The mixture was stirred at reflux under dinitrogen and monitored by TLC (95 DCM/5 MeOH). After 2 hours at reflux, the mixture was cooled and diluted with Et<sub>2</sub>O (3 mL) and H<sub>2</sub>O (2 mL). The organic phase was collected, washed with brine (0.5 mL), dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The product was purified by column chromatography (SiO<sub>2</sub>, eluent: DCM/MeOH from 100 to 97.5:2.5) to give 171 mg of *N*-(*t*-butyl)-*N*-(2-((2-(hexylthio)ethyl)amino)-2-oxoethyl)acetamide as yellowish oil. Yield: 82%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.55 (br s, 1H), 3.96 (s, 2H), 3.50 (dt, 2H, *J* = 6.3, 6.0 Hz), 2.68 (t, 2H, *J* = 6.3 Hz), 2.50 (t, 2H, *J* = 2.5 Hz), 2.10 (s, 3H), 1.62–1.51 (m, 2H), 1.46 (s, 9H), 1.40–1.23 (m, 6H), 0.88 (t, 3H, *J* = 6.9 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.5, 169.9, 57.9, 50.3, 38.0, 31.9, 31.7, 31.5, 29.7, 28.9, 28.6, 25.4, 22.6, 14.1; HRMS (ESI) calcd. for C<sub>16</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>NaS [M+Na]<sup>+</sup>: 339.2077, found: 339.2076.

*N*-(*tert*-butyl)-*N*-(2-oxo-2-((3-phenylprop-2-yn-1-yl)amino)ethyl)acetamide (7a). In a two-necked round bottom flask, with a stirring bar, an air condenser and under dinitrogen, was added the  $PdCl_2(PPh_3)_2$  (49 mg, 0.07 mmol, 8% mol equiv.), Cul (27 mg, 0.14 mmol, 16% mol equiv.), PPh<sub>3</sub> (37 mg, 0.14 mmol, 16% mol equiv.), and the *N*-(*tert*-butyl)-*N*-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)acetamide **4b** (180 mg, 0.85 mmol, 1 equiv.). A degassed solution of NEt<sub>3</sub> (0.3 mL), iodobenzene (346 mg, 1.70 mmol, 2 equiv.) in THF (3.0 mL) was added to the mixture. The mixture was stirred at reflux under dinitrogen atmosphere during 5.5 hours to give a dark red solution and was monitored with TLC (95:5 dichloromethane:MeOH). The mixture was concentrated in vacuo to give a dark brown oil. Purification by column chromatography (SiO<sub>2</sub>, eluent: DCM/MeOH from 100 to 98.5:1.5) gave compound **7a** (128 mg, 53% yield) as an orange oil. <sup>1</sup>H RMN (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.40–7.37 (m, 2H), 7.31–7.26 (m, 3H), 6.43 (br s, 1H), 4.32 (d, 2H, *J* = 5.4 Hz), 4.01 (s, 2H), 2.12 (s, 3H), 1.47 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.6, 169.7, 131.8, 128.7, 128.5, 122.4, 84.1, 83.9, 58.1, 50.2, 30.2, 28.9, 25.5; HRMS (ESI) calcd. for  $C_{17}H_{22}N_2O_2K$  [M+K]<sup>+</sup>: 325.1313, found: 325.1313.

#### N-(tert-butyl)-N-(2-(((1-(4-(tert-butyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-2-oxoethyl)aceta-

**mide (7b).** In a two-necked round-bottom flask, with a stirring bar, an air condenser and under dinitrogen, was added at room temperature PPh<sub>3</sub> (5 mg, 0.02 mmol, 2% mol equiv.), Cul (2 mg, 0.01 mmol, 1% mol equiv.) and *N*-(*tert*-butyl)-*N*-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)acetamide **4b** (210 mg, 1.00 mmol, 1 equiv.). A degassed solution of DIPEA (387 mg, 3.00 mmol, 3 equiv.), 4-(*tert*-butyl)benzyl azide (189 mg, 1.00 mmol, 1 equiv.) in toluene (5 mL) was added to the mixture. The mixture was stirred at reflux under argon atmosphere during 15.5 hours and was monitored with TLC (93:7 dichloromethane:MeOH). Compound **4b** was not fully consumed. The mixture was concentrated in vacuo to give a dark green viscous residue. Purification by column chromatography (SiO<sub>2</sub>, eluent: DCM/MeOH from 100 to 97.5:2.5) gave **7b** (350 mg, 88%) as a beige solid, mp: 118 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45 (br s, 1H), 7.38 (d, 2H, *J* = 8.2 Hz), 7.19 (d, 2H, *J* = 8.2 Hz), 6.83 (br s, 1H), 5.46 (s, 2H), 4.54 (br s, 2H), 3.95 (s, 2H), 2.02 (s, 3H), 1.37 (s, 9H), 1.30 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.5, 170.1, 152.1, 144.7, 131.4, 127.9, 126.1, 122.2, 57.8, 54.1, 49.9, 34.9, 34.7, 31.3, 28.7, 25.4; HRMS (ESI) calcd. for C<sub>22</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup>: 422.2527, found: 422.2526.

### 2- NMR SPECTRA



Figure S1. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) NMR spectrum of (4a) recorded at 23 °C.



Figure S2.  ${}^{13}C{}^{1}H{}$  (100 MHz, CDCl<sub>3</sub>) NMR spectrum of (4a) recorded at 23 °C.



Figure S3. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) NMR spectrum of (4b) recorded at 23 °C.



Figure S4. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CDCl<sub>3</sub>) NMR spectrum of (4b) recorded at 23 °C.



Figure S5. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) NMR spectrum of (4c) recorded at 23 °C.



Figure S6.  ${}^{13}C{}^{1}H{}$  (100 MHz, CDCl<sub>3</sub>) NMR spectrum of (4c) recorded at 23 °C.



Figure S7. <sup>1</sup>H (400 MHz, DMSO-d6) NMR spectrum of (4d) (Cis/Trans:39/61) recorded at 23 °C.







Figure S9. NOESY (400 MHz, DMSO-d6) NMR spectrum of (4d) (Cis/Trans:39/61) recorded at 23 °C.



Figure S10. <sup>1</sup>H (400 MHz, DMSO-d6) NMR spectrum of (4e) (Cis/Trans:38/62) recorded at 23 °C.



Figure S11. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, DMSO-d6) NMR spectrum of (4e) (Cis/Trans:38/62) recorded at 23 °C.



Figure S12. NOESY (400 MHz, DMSO-d6) NMR spectrum of (4e) (Cis/Trans:38/62) recorded at 23 °C.



Figure S13. <sup>1</sup>H (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) NMR spectrum of (5a) recorded at 23 °C.



Figure S14. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) NMR spectrum of (5a) recorded at 23 °C.



Figure S15. <sup>1</sup>H (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) NMR spectrum of (5b) recorded at 23 °C.



Figure S16. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) NMR spectrum of (5b) recorded at 23 °C.



Figure S17. <sup>1</sup>H (400 MHz, acetone-d6) NMR spectrum of (5c) recorded at 23 °C.



Figure S18. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, acetone-d6) NMR spectrum of (5c) recorded at 23 °C.



Figure S19.  $^{1}$ H (400 MHz, CDCl<sub>3</sub>) NMR spectrum of (6a) recorded at 23 °C.



Figure S20. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CDCI<sub>3</sub>) NMR spectrum of (6a) recorded at 23 °C.



Figure S21. <sup>1</sup>H (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) NMR spectrum of (6b) recorded at 23 °C.



Figure S22. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) NMR spectrum of (6b) recorded at 23 °C.



Figure S23. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) NMR spectrum of (6c) recorded at 23 °C.



Figure S24. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CDCl<sub>3</sub>) NMR spectrum of (6c) recorded at 23 °C.



Figure S25. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) NMR spectrum of (7a) recorded at 23 °C.



Figure S26. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CDCI<sub>3</sub>) NMR spectrum of (7a) recorded at 23 °C.



Figure S27. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) NMR spectrum of (7b) recorded at 23 °C.



Figure S28. <sup>13</sup>C{<sup>1</sup>H} (100 MHz, CDCl<sub>3</sub>) NMR spectrum of (7b) recorded at 23 °C.

#### **3- CRYSTALLOGRAPHIC DATA**

Single crystal diffraction data were collected on a D8 Venture Bruker AXS diffractometer with multilayers monochromatized Mo-K $\alpha$  radiation. Structures were solved by dual-space algorithm using SHELXT program<sup>2</sup> and then refined with full-matrix least-squares methods based on  $F^2$  (SHELXL program).<sup>3</sup> All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Except nitrogen linked hydrogen atoms that were introduced in the structural model through Fourier difference maps analysis, H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters.



Compound 4d.

Crystal data (CCDC 2088057): C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>, M = 182.22 g.mol<sup>-1</sup>, T = 150(2) K, monoclinic, space group =  $P 2_1/n$ , a = 7.7318(15) Å, b = 7.9949(13) Å, c = 16.678(3) Å,  $\beta$  = 102.593(10)°, V = 1006.2 (3) Å<sup>3</sup>, Z = 4, Dc = 1.203 g.cm<sup>-3</sup>, absorption coefficient = 0.086 mm<sup>-1</sup>, F(000) = 392, reflections collected = 6273, independent reflections = 2282 (Rint = 0.0226), data/restraints/parameters = 2282/0/122. Final R indices (I > 2 $\sigma$ ): R1 = 0.0385. R indices (all data): wR2 = 0.1092, goodness-of-fit on F<sup>2</sup> of 1.135.



**Figure S29.** X-ray structure of compound **4d** with packing and cell axes (left) and isolated (right). Hydrogens are omitted for clarity; ellipsoid are drawn with 50% probability.

<sup>&</sup>lt;sup>2</sup> G. M. Sheldrick, Acta Cryst. 2015, A71, 3-8

<sup>&</sup>lt;sup>3</sup> G. M . Sheldrick, Acta Cryst. 2015, C71, 3-8



Compound 6a.

Crystal data (CCDC 2054094):  $C_{16}H_{24}N_2O_2S$ , M = 308.43 g.mol<sup>-1</sup>, T = 296(2) K, monoclinic, space group =  $P 2_1/n$ , a = 8.7017(4) Å, b = 13.4179(6) Å, c = 14.9669(8) Å,  $\beta$  = 101.018(2)°, V = 1715.30(14) Å<sup>3</sup>, Z = 4, Dc = 1.194 g.cm<sup>-3</sup>, absorption coefficient = 0.195 mm<sup>-1</sup>, F(000) = 664, reflections collected = 13887, independent reflections = 3929 (Rint = 0.0489), data/restraints/parameters = 3929/0/198. Final R indices (I > 2 $\sigma$ ): R1 = 0.0598. R indices (all data): wR2 = 0.1502, goodness-of-fit on F<sup>2</sup> of 0.956.



**Figure S30.** X-ray structure of compound **6a** with packing and cell axes (left) and isolated (right). Hydrogens are omitted for clarity; ellipsoid are drawn with 50% probability.



Compound 7b.

Crystal data (CCDC 2054093):  $C_{22}H_{33}N_5O_2$ , M = 399.53 g.mol<sup>-1</sup>, T = 150(2) K, monoclinic, space group =  $P 2_1/c$ , a = 5.7714(5) Å, b = 10.1962(9) Å, c = 37.781(3) Å,  $\alpha = 90^\circ$ ,  $\beta = 93.849(3)^\circ$ ,  $\gamma = 90^\circ$ , V = 2218.2(3) Å<sup>3</sup>, Z = 4, Dc = 1.196 g.cm<sup>-3</sup>, absorption coefficient = 0.079 mm<sup>-1</sup>, F(000) = 864, reflections collected = 25469, independent reflections = 4972 (Rint = 0.0488), data/restraints/parameters = 4972/0/272. Final R indices (I > 2\sigma): R1 = 0.0496. R indices (all data): wR2 = 0.1235, goodness-of-fit on F<sup>2</sup> of 1.035.



**Figure S31.** X-ray structure of compound **7b** with packing and cell axes (left) and isolated (right). Hydrogens are omitted for clarity; ellipsoid are drawn with 50% probability.